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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/975,036	SHORT ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-211* is/are pending in the application.

4a) Of the above claim(s) *47-211* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-46 in the response of August 22, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Objections

2. Claims 20, 21 and 29 are objected to because of the following informalities:

In claim 20, "The method of claim –1" should read "The method of claim 1".

In claim 21, "The method of claim –2" should read "The method of claim 2".

In claim 29, "biomolecume" should read "biomolecule."

Specification

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

The specification lacks antecedent basis for the concept of labeling the nucleic acid probe with a biotinylated substrate wherein the biotinylated substrate comprises a core fluorophore, a spacer connected to the florophore by a first connector and connector to a bioactivity or biomolecule of interest and 2 functional groups or wherein the biotinylated substrate comprises a core fluorophore, a spacer connected to the fluorophore by a connector and connected to a bioactivity or biomolecule of interest by a second connector, and a quencher component attached to a fluorophore by a polymer.

While the specification discusses microdroplets having a biotinylated substate that forms a biotin-streptavidin-biotin bridge and the specification discusses GMD-attachable fluorogenic substrates and GMD-attachable fluorescence resonance energy transfer substrates, the specification does not discuss attaching such a biotinylated substrates to nucleic acid probes and using such probes for hybridization and detection purposes.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-33 and 35-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying a polynucleotide by contacting a plurality of polynucleotides derived from an organism with a nucleic acid probe labeled with a fluorophore or with biotin, does not reasonably provide enablement for methods for identifying a polynucleotide by contacting a plurality of polynucleotides derived from an organism with a nucleic acid probe labeled with a biotinlyated substrate wherein said biotinylated substrate may comprise a core fluorophore, connectors, spacers, quenchers, functional groups and / or a polymer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the

nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods for identifying a polynucleotide by contacting a plurality of polynucleotides derived from an organism with a nucleic acid probe labeled with a biotinylated substrate wherein the biotinylated substrate may comprise a core fluorophore, a spacer connected to the florophore by a first connector and a connector to a bioactivity or biomolecule of interest and 2 functional groups or wherein the biotinylated substrate comprises a core fluorophore, a spacer connected to the fluorophore by a connector and connected to a bioactivity or biomolecule of interest by a second connector, and a quencher component attached to a fluorophore by a polymer. The specification teaches methods for detecting a polynucleotide of interest wherein the polynucleotide is encapsulated and the method includes contacting the polynucleotide with a nucleic acid probe labeled with a detectable moiety, forming a hybridization complex between the polynucleotide and the probe and detecting the detectable moiety as indicative of the presence of the hybridization complex and thus indicative of the presence of a polynucleotide of interest. In addition, the specification (pages 126-128) teaches methods for detecting a polynucleotide of interest using a gel microdroplet (GMD) modified to contain biotin-labeled agarose. A biotinylated substrate is added to the GMD and the biotinylated substrate is captured within the GMD by forming a bridge of biotin-streptavidin-biotinylated-substrate. If a bacterial cell contains a particular

enzyme, the enzyme will hydrolyze a fluorescent substrate and the fluorescent substrate is retained within the GMD via the biotin-streptavidin-biotin bridge. The specification also provides the structure for a GMD-attachable fluorogenic substrate and a GMD-attachable fluorescence resonance energy transfer substrate. However, the specification does not teach methods in which the biotinylated substrate is attached to a nucleic acid probe. There is no disclosure in the specification to provide guidance as to how to practice a method in which a probe labeled with a biotinylated substrate is hybridized to polynucleotides within a cell or "microenvironment" and the presence of the biotinylated substrate is detected as indicative of hybridization and the presence of the polynucleotide of interest. There is also no disclosure in the specification of forming a bridge between the biotin (presumably directly attached to the nucleic acid probe) and the steptavidin and reacting this complex with an undescribed enzyme and then detecting the biotinylated substrate as indicative of the presence of the polynucleotide of interest. While the skilled artisan does know how to use fluorescent labeled probes, enzyme labeled probes, FRET labeled probes and biotinylated probes, use of such probes is distinct from the use of probes that contain multiple attachment groups of fluorophores, quenchers, spacers, connectors, polymers, biotin, and "bioactivity or biomolecules of interest." The specification does not exemplify nor does it provide sufficient teachings and guidance as to how to employ such complexes in hybridization methods to detect a polynucleotide of interest. Accordingly, the specification has not adequately taught one of skill in the art how to use the invention as it is broadly claimed without undue experimentation.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-46 are indefinite because it is not clear as to what is intended to be the relationship between the individual method steps and it is unclear as to how the individual method steps relate to the method of identifying a polynucleotide. The claims are drawn to methods of identifying a polynucleotide and include the steps of contacting polynucleotides with probes labeled with a detectable molecule under conditions that allow hybridization of the probe to the polynucleotide and then identifying a polynucleotide of interest by detecting the detectable molecule. The claims do not include any wash or separation step to remove unbound labeled probes. Additionally, the claims do not clarify whether the method detects the polynucleotides hybridized to the probe or if the method merely detects the labeled probe added to a sample containing polynucleotides. It is also unclear as to whether there is intended to be a distinction between the polynucleotide and the "polynucleotide of interest." Lastly, while the preamble recites "in a liquid phase," the method steps do not require a liquid phase. Therefore, it is not clear as to whether the recitation in the preamble is intended to further limit the claims. This recitations is further unclear in view of the fact that claims 25-41 require that the polynucleotide is encapsulated in a microenvironment such as a

cell or agarose or bead. It is unclear as to how the environment of a cell considered to be a "liquid solution."

Claim 14 is indefinite over the recitation of "the dielectric signature of the clone" because this phrase lacks proper antecedent basis. While the claim previously refers to polynucleotides, the claim does not previously refer to clones. It is not clear as to what is intended to be meant by a molecule that modulates the dielectric signature of the clone.

Claim 25 is indefinite over the recitation of "further comprising encapsulation of the polynucleotide in a microenvironment" because it is not clear as to whether this step is performed prior to or after step a or b and it is not clear as to whether "the polynucleotide" refers to "the plurality of polynucleotides derived from at least one organism" or to "the polynucleotides having complementary sequences" or "the polynucleotides of interest."

Claims 29-33 and 35-40 are indefinite over the recitation of "functional groups" because the claims do not set forth the properties or activities of the functional groups. It is not clear as to whether the functional groups may be any molecule or whether these groups have some specific, yet unstated function.

In claims 29-33 and 35-40, the phrase "the bioactivity or biomolecule of interest" lack proper antecedent basis. It is unclear as to what constitutes the bioactivity or biomolecule of interest and it is unclear as to what is intended to be the relationship between the bioactivity/biomolecule of interest and the polynucleotide of interest. It is also unclear as to how the bioactivity or biomolecule is utilized in the detection method.

Claim 32 is indefinite over the recitation of "selected from the groups consisting of" because this is improper Markush language and the claim does not recite groups, but rather recites function moieties.

In claim 35, the phrase "the clourophore" lacks proper antecedent basis.

Claim 43 is indefinite over the phrase "encodes a small molecule." The term small is a relative term, yet the claim does not set forth what the molecule is small in comparison to. The term "small" is not defined in the specification and the phrase "small molecule" does not have a defined meaning in the art. Accordingly, one cannot determine the meets and bounds of the claimed subject matter.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-28, 34, and 41-46 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 32-60 of copending Application No. 09/738,871. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims

and the claims of '871 both encompass methods for detecting a polynucleotide of interest by contacting polynucleotides from a mixed population of cells from an environmental sample with a detectably labeled polynucleotide probe and detecting the detectable labeled. Both the present claims and the claims of '871 include encapsulation of the polynucleotide and detecting the detectable label using an analyzer such as FACS.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 1-28, 34, and 41-46 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-52 of copending Application No. 09/685,432. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '432 both encompass methods for detecting a polynucleotide of interest by contacting polynucleotides from a mixed population of cells from an environmental sample with a detectably labeled polynucleotide probe and detecting the detectable labeled. Both the present claims and the claims of '432 include encapsulation of the polynucleotide and detecting the detectable label using an analyzer such as FACS.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 1-28, 34, and 41-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S.

Patent No. 6,174,673. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '673 are both inclusive of methods for identifying biomolecules by screening genomic DNA wherein the methods comprise providing an expression library from a mixed population of organisms, encapsulating a bioactive fluorescent substrate with a clone of the library, screening the encapsulated material with a fluorescent analyzer and identifying clones wherein fluorescence indicates DNA that encodes a biomolecule. The present claims are limited to methods which detect a polynucleotide. However, the generic recitation in the claims of '673 of "biomolecule" includes polynucleotides. Additionally, it is noted that the claims of '673 generically recite contacting the expression library with a "bioactive fluorescent substrate." Reading the claims of '673 in light of the disclosure of '673, the phrase "bioactive fluorescent substrate" is inclusive of polynucleotides comprising a fluorescent label. It is further noted that the present claims do not require a specific hybridization step or detection of hybridization and thereby are inclusive of the method generically recited in the claims of '673 of contacting a DNA library with a bioactive fluorescent substrate (i.e. fluorescently labeled probe) and detecting fluorescence as a means of identifying a biomolecule (i.e., polynucleotide).

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the

applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 15, 16, 19-27 and 41-46 rejected under 35 U.S.C. 102(e) as being anticipated by Thompson et al (U.S. Patent NO. 5,824,485).

Thompson teaches a method for detecting a polynucleotide wherein the method comprises contacting a plurality of polynucleotides derived from at least one organism with a detectably labeled probe under hybridization conditions and identifying hybridization between the probe and the polynucleotide as indicative of the presence of the polynucleotide of interest (see, for example, column 37: "The combinatorial gene expression libraries of the invention may be pre-screened or screened by a variety of methods, including but not limited to, visual inspection, automated image analysis, hybridization to molecular beacon DNA probes (Tyagi et al. 1996, Nature Biotechnol, 14:303-308), fluorescence activated cell sorting (FACS) and magnetic cell sorting (MACS)"; see also columns 31-32, section 5.1.6; and column 41, section 5.3.5: "(t)he isolated double-stranded DNA representing non-primary metabolism related genes may then be labeled using random priming, and used as a probe to pre-screen the library.")

With respect to claims 2-5 and 19-22, Thompson (column 26) teaches that "(t)he present invention relates to the construction and uses of combinatorial gene expression libraries, wherein the host organisms contain genetic material encoding natural biochemical pathways or portions thereof that is derived from a plurality of species of donor organisms, and are capable of producing functional gene products of the donor organisms. Biochemical pathways or portions thereof are thus functionally reconstituted

in individual host organisms of a library." At column 12, Thompson states that any eukaryotic or prokaryotic organism or virus can be a donor organism for the purpose of preparing combinatorial gene expression libraries and in particular the libraries may be prepared from environmental samples, such as soil and marine sediments (column 13).

With respect to claim 15 and 16, Thompson teaches using FACS or magnetic cell sorting (MACS) to detect the detectable molecule (see column 33, 35 and 37).

With respect to claims, 23 and 24, Thompson teaches that the library may be prepared from an extremophile such as an acidophile, halophile or thermophile (see column 14).

With respect to claims 25-27, Thompson (columns 34-38) also teaches encapsulating the polynucleotide of interest. For instance, Thompson (column 34-35) states that "(t)he present invention also provides encapsulation as an efficient high-throughput method for growing cells in a confined space...Another advantage of encapsulation is the ability to co-encapsulate components of the reporter regimen and/or other indicator cells with library cells so that prescreening or screening can be performed in a discreet unit." At column 37, Thompson teaches that encapsulation may be performed by producing microdroplets using semisolid matrices such as agarose.

With respect to claims 41-46, Thompson (columns 9-10) states that "gene expression libraries comprising complete naturally occurring biochemical pathways or substantial portions thereof can greatly facilitate searches for donor multi-enzyme systems responsible for making compounds or providing activities of interest. Further, claim 9 of Thompson states that the polynucleotide of interest may comprise one or

more operons or portions thereof of the donor microorganism. In particular, with reference to claim 46, Thompson teaches that the libraries contain polynucleotides encoding proteins of the bacterial polyketide synthases (PKSs) pathway (see column 4, paragraph 2).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 14-16, 19-28, 34 and 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson in view of Blumenfeld (US Patent No. 6,228,580).

The teachings of Thompson are presented above. While Thompson teaches labeling probes and particularly teaches labeling probes with molecular beacons,

Thompson does not teach the length of such probes and does not specifically teach labeling the probes with a fluorophore or biotinylated substrate.

Blumenfeld teaches that nucleic acid hybridization probes may be of a length of 100 to 1000 nucleotides (see, for example, column 3). The probes may also be of a larger length since large probes confer greater specificity of hybridization (column 3). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used probes of the length of 100 to 1000 or up to 5000 nucleotides or more in the method of Thompson in order to have increased the specificity of hybridization and therefore increased the specificity of the method of detecting a polynucleotide of interest.

Further, Blumenfeld teachings labeling nucleic acid hybridization probes with fluorescent moieties (see for example column 5-6). The reference also teaches using biotinylated probes and probes labeled with biotin-DIG (columns 6-7). Thompson teaches that biotin labeled nuc ic acids can be detected u tavidin or by an anti-biotin antibody coupled to an enzyme (column 6). Nucleotides labeled with biotin and biotin-DIG are considered to be biotinylated substrates. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have labeled the probes of Thompson with the fluorescent or biotin moieties taught by Blumenfeld in order to have facilitated the detection of the probe and thereby the detection of the polynucleotide of interest.

9. Claims 1-10, 13, 14, 16, 18-27, and 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson in view of Hefti (US Patent No. 6,340,568).

The teachings of Thompson are presented above. Thompson does not teach the length of the nucleic acid probe and does not teach detecting the nucleic acid by multipole coupling spectroscopy (MCS).

However, Hefti teaches that nucleic acid hybridization probes may be short in length such as 50-100 base pairs long, or may be of a longer length ranging up to 1,000-10,000 nucleotides (see, for example, column 54-55). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used probes of the length of 50-100 to 1,000 or up to 10,000 nucleotides in length in the method of Thompson since Hefti teaches that probes of this length may be used to effectively detect the presence of a polynucleotide of interest.

Additionally, Hefti teaches methods for detecting nucleic acid hybridization between a probe and a complementary target sequence using a method of multipole coupling spectroscopy (see, for example, columns 13-14 and 23). Hefti (columns 25-26) teaches that "(t)he de ection and identification of molecular binding c be accomplished by detecting and measuring the dielectric properties at the m olecular level. The dielectric properties at the molecular level can be defined by the molecule's multipole moments." The reference teaches that while MCS can be performed using labeled probes, labeling of probes with additional moieties, such as fluorophores, is not necessary. If the probes are not labeled with moieties such as fluorophores, this provides the advantage of avoiding steric hindrance caused by the presence of the label and prevents background signal that results from incomplete removal of unbound labeled probes (see column 47). Accordingly, it would have been obvious to one of

ordinary skill in the art at the time the invention was made to have modified the method of Thompson so as to have detected hybridization between the probe and the polynucleotide of interest using the multipole coupling spectroscopy method of Hefti in order to have achieved the advantages set forth by Hefti of generating a highly effective and sensitive method for detecting the presence of a target polynucleotide of interest.

10. Claims 1-17, 19-28, 34 and 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson in view of Blumenfeld (US Patent No. 6,228,580) and further in view of Baselt (U.S. Patent No. 5,981,297).

The teachings of Thompson and Blumenfeld are presented above. The combined references do not teach labeling the nucleic acid probe with a magnetic molecule and do not teach detection of the nucleic acid probe with a Super Conducting Quantum Interference (SQUID) device.

However, Baselt teaches labeling nucleic acid probes with magnetic molecules and detecting hybridization of probes to polynucleotides of interest using SQUID (see column 2-4). Baselt teaches that the magnetic field sensors of the SQUID device provide for an increase in sensitivity several orders of magnitude higher than conventional detection methods (see column 4). The method is also faster than conventional detection methods and can be automated.

In view of the teachings of Baselt, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Thompson so as to have labeled the probes with magnetic molecules and to have detected hybridization of the probe to complementary nucleic acids using SQUID in

order to have achieved the benefits set forth by Baselt of providing a faster, more sensitive method for detecting a polynucleotide of interest, wherein the method could be automated.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. This phone number will be changed after January 13 to (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
December 4, 2003

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER